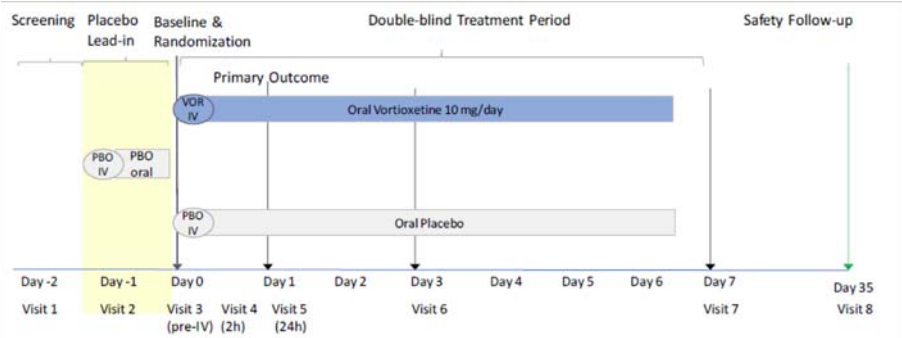
Synopsis – Study 17915A

Study Title Interventional, randomized, double-blind, placebo-controlled study of the efficacy and safety of initial administration of 25 mg vortioxetine intravenously with 10 mg/day vortioxetine orally in patients with Major Depressive Disorder	
Investigators 13 principal investigators at 13 sites in 3 countries *Signatory investigator* – [redacted]	
Study Sites 2 sites in Estonia, 3 sites in Latvia and 8 sites in Bulgaria	
Publication None (as of the date of this report)	
Study Period *First patient first visit* – 3 December 2018 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 28 August 2019 (the date of the last protocol-specified contact with any patient)	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objectives • to evaluate the efficacy of vortioxetine 25 mg intravenously (IV) (single initial dose) administered with a vortioxetine 10 mg/day oral dose regimen on depressive symptoms	**Depressive symptoms** • Primary endpoint: – change from Baseline (Day 0) to Day 1 (24 hours post-infusion) in Montgomery and Åsberg Depression Rating Scale (MADRS)-6 subscale score • Key secondary endpoint: – change from Baseline (Day 0) to Day 3 in MADRS-6 subscale • Secondary endpoints: – change from Baseline (Day 0) to Day 7 in MADRS-6 subscale score – change from Baseline in MADRS total score at each visit – response (defined as a ≥50% decrease in MADRS total score from Baseline) on Days 1 and 3 • Exploratory endpoints: – response (defined as a ≥50% decrease in MADRS total score from Baseline) on Day 7 – remission at each visit (defined as a MADRS total score ≤10) – Area under the Curve (AUC) of MADRS-6 subscale score change from Baseline to Day 7 – AUC of MADRS total score change from Baseline from Baseline to Day 7 – change from Baseline in each item of the MADRS total score at each visit – change from Baseline in Hospital Anxiety and Depression Scale (HADS) depression subscale score at each visit – Patient Global Impression of Change (PGIC) score on each day from Baseline until Day 7

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Secondary Objectives • to evaluate the efficacy of vortioxetine 25 mg IV (single initial dose) administered with a vortioxetine 10 mg/day oral dose regimen on global clinical impression	**Global Clinical Impression** • Secondary endpoints: – Clinical Global Impression - Global Improvement (CGI-I) score relative to Baseline at each post-Baseline visit – CGI-I response (defined as CGI-I score ≤2) on Days 1 and 3 – change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) score at each visit • Exploratory endpoints: – CGI-S remission (CGI-S score ≤2) at each visit – CGI-I response (defined as CGI-I score ≤2) relative to Baseline on Day 7
• to determine population pharmacokinetics parameters of vortioxetine	**Pharmacokinetics** • Secondary endpoints: – population pharmacokinetic parameter values
Exploratory Objectives • to explore the effect of vortioxetine 25 mg IV (single initial dose) administered with a vortioxetine 10 mg/day oral dose regimen on anxiety • to explore the effect of vortioxetine 25 mg IV (single initial dose) administered with a vortioxetine 10 mg/day oral dose regimen on suicidal ideation • to explore associations between inflammatory biomarkers and clinical variables[a]	**Exploratory Endpoints:** • change from Baseline in HADS anxiety subscale score at each visit • change from Baseline in Clinical Global Impression – Severity of Suicidality (CGI-SS) score at each visit • CGI-SS improvement score relative to Baseline at each visit
Safety Objectives • to evaluate the safety and tolerability of vortioxetine 25 mg IV (single initial dose) administered with a vortioxetine 10 mg/day oral dose regimen	**Safety Endpoints** • adverse events • absolute values and changes from Baseline in clinical safety laboratory test values, vital signs and electrocardiogram (ECG) evaluations • Potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, and ECG evaluation • Columbia-Suicide Severity Rating Scale (C-SSRS) score
a Samples were collected for possible future exploratory analyses.	

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, randomized, double-blind, placebo-controlled fixed-dose study.
- The study consisted of:
  - Screening Period (Day -2 to Day -1)
  - Placebo Lead-in Period - one day single-blind treatment with placebo (PBO) (Day -1)
  - Treatment Period – 7-day Double-blind Treatment (DBT) Period with PBO or vortioxetine (VOR) (Day 0 to Day 6)
  - Safety Follow-up Period – 4-week period after completion of the study
- The study design is presented below.



- Patients were randomized 1:1 to either of the following two dose regimens:
  - vortioxetine 25 mg single dose (IV) on Day 0 and vortioxetine 10 mg/day tablets once daily for 7 days
  - placebo single dose (IV) on Day 0 and placebo tablets once daily for 7 days
- Efficacy data were collected at Baseline and Visits 5, 6 and 7.
- At Visits 4, 5 and 7, blood samples were drawn for drug concentration analysis of vortioxetine.
- Safety assessments were performed throughout the study.

Number of Patients Planned

80 patients were planned for randomization: 40 patients in the VOR group and 40 patients in the PBO group.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of recurrent major depressive disorder (MDD) according to DSM-5® criteria, who:

- had a MADRS total score ≥30 points at the Screening Visit
- were ≥18 and ≤65 years of age
- had had the current major depressive episode (MDE) for ≥3 months, but less than 12 months
- had received treatment for the current MDE with an selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor(SNRI) monotherapy (citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, sertraline) at an approved therapeutic dose for at least 6 weeks
- as part of standard-of-care treatment, was to be admitted to hospital due to the severity of the depressive symptoms and who was willing to remain hospitalized for the duration of the study treatment period

Investigational Medicinal Products (IMPs), Doses and Modes of Administration, Batch Numbers

Vortioxetine – 25 mg, IV infusion of 25 mL 1 mg/mL concentrate for solution for infusion; batch No 2575715

Vortioxetine – 10 mg/day, film-coated tablets, orally; batch No 2574135

Control Products, Doses and Modes of Administration, Batch Numbers

Placebo – IV infusion of concentrate for solution for infusion; batch No 2575725

Placebo – film-coated tablets, orally; batch No 2558025

Duration of Treatment

8 days (1 day PBO Lead-in Period; 7 days DBT Period)

Statistical Methodology

- For all clinical outcome assessment tools (except the C-SSRS) and for ECGs, laboratory tests, and vital signs, two baselines were defined and referred to as:
  - Enrolment – the value captured either at the Screening Visit (Day -2) or at Visit 2 (Day -1), whichever is later
  - Baseline – the value captured at Visit 3 (Day 0)
- The following analysis sets were used:
  - *all-patients enrolled set* (APES) – all patients enrolled to the PBO Lead-in Period
  - *all-patients-treated set A* (APTS_A) – all patients in the APES who received at least one dose of IMP in the PBO Lead-in Period
  - *all-patients randomized set* (APRS) – all patients randomized in the DBT Period
  - *all-patients-treated set* (APTS) – all patients in the APRS who received IMP post-randomization
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid Baseline assessment of the MADRS-6 subscale score and a valid post-Baseline assessment of the MADRS-6 subscale score and who received the IV infusion and at least one dose of oral IMP
- Unless otherwise indicated, the efficacy analyses were based on the FAS, and the safety analyses were based on the APTS.
- All data collected are tabulated and/or listed, as appropriate. The presentation of results may also include plots. The data from the clinical assessments are summarized using descriptive statistics.
- The primary efficacy analysis was a mixed model for repeated measures (MMRM) of the change from Baseline to Day 1 in MADRS-6 subscore scale. The model included the following fixed effects: site, Day (1, 3, and 7), and treatment; the Baseline MADRS-6 subscale score as a continuous covariate; and the treatment-by-Day interaction; and the Baseline score-by-day interaction. The analysis was based on the missed at random (MAR) assumption including all available observations (observed cases [OC] data).
- The key secondary and secondary efficacy analysis of the continuous variables (change from Baseline in MADRS-6 subscale score, change from Baseline in MADRS total score, CGI-I score relative to Baseline, and change from Baseline in CGI-S score) were performed using the same methodology (FAS, MMRM) as for the primary efficacy variable. For analyses of CGI-I the Baseline measure for CGI-S was included as baseline assessment covariate. Response and remission were analysed using logistic regression with treatment as factor and the Baseline score as a covariate (FAS, OC).
- As a sensitivity analysis, the primary and key secondary endpoints were tested using an analysis of covariance (ANCOVA) adjusting for Baseline score, site, treatment, and performed on (FAS, OC) and on (FAS, last observation carried forward [LOCF]).
- Two exploratory analyses were performed to further analyse the change from Baseline in MADRS-6 subscale score until Day 7, as well as the change from Baseline in MADRS total score until Day 7: a non-linear mixed effects model based on the E_{max} model, and the AUC calculated following the trapezoidal rule.
- The exploratory analysis of the continuous variables (change from Baseline in HADS depression and anxiety subscale score, PGIC score, and change from Baseline in each of the MADRS items) were performed using the same methodology (FAS, MMRM) as for the primary efficacy variable, except that for the PGIC score all measurements from Baseline to Day 7 were used and the enrolment CGI-S value was included as Baseline assessment covariate.
- A hierarchical testing procedure was used. It was first tested if the improvements on Day 1 based on the primary endpoint were the same in the two treatment groups. If this hypothesis was rejected and the numerical improvement on Day 1 was greater in the VOR group than in the PBO group, the key secondary endpoint would be tested. Both tests are two-sided and on a significance level of 0.05.

Statistical Methodology (continued)

- Unless otherwise specified, all the safety data presentations are based on the APTS_A for the PBO Lead-in Period and the APTS for the DBT Period. In all the tables and figures, the safety data are presented by treatment group.
- The treatment-emergent adverse events (TEAEs) of special interest were summarized by treatment group. The following adverse events were considered of special interest, in line with the general development programme for vortioxetine; TEAEs related to nausea, vomiting, rash, pruritus, itching, diarrhoea, constipation, and sexual dysfunction. Adverse events relating to the injection site were also considered of special interest for this study, given the new mode of administration included in the study.
- The C-SSRS was assessed using the C-SSRS *Baseline/Screening Version* (lifetime and past 6 months) and *Since Last Visit Version* (for post-Baseline assessments). For each period, the most severe event per patient related to *suicidal ideation* and *suicidal behaviour* was summarized. *Non-suicidal self-injurious behaviour* was considered separately. Missing C-SSRS scores were not imputed.
- The suicidality was assessed using the CGI-SS score in two ways; the change from Baseline in CGI-SS score at each visit, and the CGI-SS improvement score relative to Baseline at each visit. The same methodology as that described for the primary and key secondary endpoints were used. For analyses of CGI-SS improvement score, the Baseline measure for CGI-SS was included as baseline assessment covariate.
- The results of the clinical safety laboratory test parameters in the PBO Lead-in Period and the DBT Period were summarized using descriptive statistics, both absolute values and changes from Baseline (DBT Period only). The number and percentage of patients with at least one PCS value in any of the periods were summarized. All available assessments in the period were included in the evaluation of PCS values.
- To evaluate potential drug-induced liver injury (DILI), post-randomization values for various liver tests (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [BILI], and alkaline phosphatase [ALP]) were categorized. In addition, assessment time points for patients for whom Hy's Law was potentially fulfilled was flagged in the listing:
  - ALT or AST >3x upper limits of normal (ULN) AND
  - BILI≥ 2xULN AND
  - ALP<2xULN
- Patients fulfilling any of the individual criteria in the DBT Period (ALT/AST, ALP, or BILI) were listed.

Patient Disposition and Analysis Sets

- The randomization lists, including randomization code and treatment assigned, are in Listings 1 and 2
- 81 patients were screened
- Patient disposition are summarized by analysis set and by site, respectively, in Tables 1 and 2 (PBO Lead-in Period) and Tables 3 and 4 (DBT Period). All patients who withdrew from the study are listed in Listing 3.
- Patient disposition for the PBO Lead-in Period (APES) is summarized below.

	PBO	
	n	**(%)**
Patients enrolled	81	100
Patients treated (APTS)	81	100
Patients completed	81	100
Patients withdrawn	0[a]	0

a One patient was withdrawn after completion of the PBO Lead-in Period but before randomization.

Patient Disposition and Analysis Sets, continued

- Patient disposition for the DBT Period (APRS) is summarized below.

	VOR		PBO		Total	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients randomized	39		41		80	
Patients treated (APTS)	39		41		80	
Patients completed	38	97.4	40	97.6	78	97.5
Patients withdrawn	1	2.6	1	2.4	2	2.5
Primary reason for withdrawal:						
Withdrawal of consent	1	2.6	1	2.4	2	2.5
Analysis sets:						
FAS	39		41		80	

- Patient disposition was similar across the treatment groups.

Demographics and Baseline Characteristics of the Study Population

- Demographics was similar across the treatment groups; the mean age was 47 years, the majority (73%) of the patients were women, and all but one patient were White (Table 5). The mean height, weight, and body mass index at Baseline was 169 cm, 70 kg, and 25 kg/m^2, respectively (Table 6). The drinking and smoking habits at the Screening Visit are summarized in Table 7.
- At Baseline, the patients in FAS had a mean MADRS total score of 35 points (corresponding to a *severe* depression), consistent with a mean MADRS-6 subscale score of 23 points, a mean CGI-S score of 5 points (corresponding to *markedly ill*) and a mean PGIC score of 1.4 points (Table 8).
- The mean HADS anxiety subscale score was 12 points at Baseline, and the mean HADS depression subscale score was 16 points at Baseline (Table 8). There were no notable differences in Baseline scores between the two treatment groups. The efficacy measures were also assessed at Enrolment (Table 9) and these were not notably different from the Baseline efficacy measures (Table 8).
- The patients in APTS had had 3 previous episodes of MDD on average, with a mean duration of the current MDD episode of 158 days (Table 10). The depression treatment history; the history of medical, neurological and psychiatric disorders, and the social history of the patients in ATPS are summarized in Tables 11, 12 and 13, respectively. There were no major differences between the treatment groups.
- At Baseline, 28% of the patients had relevant concurrent medical, neurological, or psychiatric disorders (Table 14). The most common disorder present in >5 patients in the ATPS were *hypertension* (13.8%) (Table 14).
- Overall, medication discontinued prior to first dose of IMP in the DBT Period (Table 15), concomitant medication continued after first dose of IMP in the DBT Period (Table 16), concomitant medication started at or after first dose of IMP in the DBT Period (Table 17), and concomitant medication started after withdrawal from treatment (Table 18) were similar across the treatment groups.

Exposure

- All 81 patients in Placebo Lead-in Period received 1 tablet of IMP for a duration of 1 day(Table 19) .
- In the DBT Period, the mean exposure was 7 tablets of IMP for a duration of 7 days (Table 20).

Efficacy Results

• The results of the analysis of the continuous primary and secondary efficacy endpoints are summarized below

Scale	Treatment	Day	N	LS mean	S.E.	Comparison to PBO (95% CI)
MADRS-6 Subscale Score	PBO	1	41	-2.76	0.60	
		3	41	-5 23	0.79	
		7	41	-7 27	0.93	
	VOR	1	39	-3.55	0.58	-0.79 (-2.19 ; 0.61)
		3	39	-5.29	0.79	-0.06 (-2.08 ; 1 97)
		7	38	-6.51	0.93	0.76 (-1.70 ; 3.21)
MADRS-10 Total Score	PBO	1	41	-4.20	0.80	
		3	41	-7.81	1.03	
		7	41	-10.63	1.26	
	VOR	1	39	-4.81	0.77	-0.61 (-2.45 ; 1.24)
		3	39	-7.47	1.01	0.34 (-2.28 ; 2.95)
		7	38	-9 38	1.26	1.24 (-2.10 ; 4.59)
CGI-I Score	PBO	1	41	3.39	0.14	
		3	41	3.12	0.14	
		7	41	2.90	0.16	
	VOR	1	39	3.34	0.13	-0.05 (-0.36 ; 0 27)
		3	39	3.08	0.14	-0.04 (-0.38 ; 0.30)
		7	38	2.84	0.16	-0.06 (-0.46 ; 0.33)
CGI-S Score	PBO	1	41	-0.33	0.09	
		3	41	-0.67	0.12	
		7	41	-1.01	0.15	
	VOR	1	39	-0.28	0.09	0.05 (-0.16 ; 0.27)
		3	39	-0.66	0.12	0.01 (-0.29 ; 0.31)
		7	38	-0 90	0.15	0.11 (-0.28 ; 0.51)

Cross-references: MADRS-6:Table 21; MADRS-10:Table 22; CGI-I:Table 23; CGI-S:Table 24

- The statistical aspects of the primary analysis were investigated. The assumption of normality as investigated by inspection of the QQ-plot (Figure 1) and the assumption of homoscedasticity of the residuals (Figure 2) were confirmed.
- There were no statistical significant difference between the two treatments in the analysis of the primary endpoint, mean change from Baseline to Day 1 in MADRS-6 subscale score. The results of the analyses of mean change from Baseline to Day 3 (key secondary endpoint) and Day 7 (secondary endpoint) in MADRS-6 subscale score corroborated the results of the primary efficacy analysis, with nominal p-values > 0.05 for both analyses. There was a decline in MADRS-6 subscale score (improvement) in both treatment groups during the treatment period (Figure 3). The sensitivity analyses of the primary endpoint were in alignment with the primary efficacy analyses (Tables 25 and 26, Figures 4 and 5).
- The results of the analyses of mean change from Baseline to Day 1, 3 and 7 in MADRS-6 subscale score in men and women (Tables 27 and 28, Figures 6 and 7) corroborated the results of the analyses in the total population, with nominal p-values > 0.05 for all of the analyses (Tables 27 and 28).
- The results of the analysis of the secondary and exploratory endpoints investigating depressive symptoms, change from Baseline in MADRS total score at Day 1, 3 and 7, corroborated the results of the primary analysis, with nominal p-values > 0.05 for all of the analyses (Table 22). There was a decline in MADRS total score (improvement) in both treatment groups during the treatment period (Figure 8).
- The results of the analysis of the change from Baseline in each item of the MADRS total score are summarized in Tables 29 to 38 and Figures 9 to 18.
- The results of the exploratory analyses, AUC of the MADRS-6 subscale score from Baseline to Day 7 and AUC of the MADRS total score from Baseline to Day 7, as well as the change from Baseline to Day 7 in MADRS-6 subscale score and MADRS total score analysed using the E_{max} model were in concordance with the results of the primary and key secondary analyses (Tables 39 and 40, Figures 19 and 20).

Efficacy Results, continued

- The results of the secondary endpoints addressing global clinical impression, CGI-I score relative to Baseline at each post-Baseline visit, and change from Baseline in CGI-S score at each visit, are summarized above and in Tables 23 and 24 and Figures 21 and 22. There were a decline (improvement) in both CGI-I score and CGI-S score in both treatment groups at all tested days (Figures 21 and 22), with nominal p-values > 0.05 for both analyses in the comparison between the two treatment groups at any of the tested days.
- The results of the analysis of patient-reported depression and anxiety symptoms are summarized above and in Tables 41 to 43 and Figures 23 to 25 . The results of these analyses corroborated those of the primary and key secondary endpoints.
- The proportion of responders and remitters with respect to depressive symptoms and global clinical impression are summarized below.

Treatment Group	**PBO**				**VOR**			
Response	**MADRS n (%)**		**CGI-I n (%)**		**MADRS n (%)**		**CGI-I n (%)**	
Day 1	0	(0)	5	(12.2)	1	(2.6)	3	(7.7)
Day 3	3	(7.3)	9	(22.0)	3	(7.7)	6	(15.4)
Day 7	8	(19.5)	13	(31.7)	5	(12.8)	11	(28.2)
Remission	**MADRS n (%)**		**CGI-S n (%)**		**MADRS n (%)**		**CGI-S n (%)**	
Day 1	0	(0)	0	(0)	0	(0)	0	(0)
Day 3	1	(2.4)	0	(0)	1	(2.6)	1	(2.6)
Day 7	4	(9.8)	2	(4.9)	3	(7.7)	2	(5.1)

Cross-reference: response: Tables 44 and 45; remission: Tables 46 and 47

- The proportion of MADRS and CGI-I responders increased during the time course of the study in both treatment groups. Both of the analyses corroborated the results of the primary analysis with nominal p-values > 0.05 between the proportion of responders in the two treatment groups. At the end of the study, at Day 7, approximately one third of the patients in each treatment group responded to the treatment according to the CGI-I definition of response (defined as CGI-I score ≤2). The proportion of MADRS and CGI-S remitters increased with time in both treatment groups, but the number of patients achieving remission of their depression according to the MADRS and CGI-S definition of remission (MADRS total score ≤10 and CGI-S score ≤2, respectively) was low in both treatment groups.
- The results of the analysis of response and remission in MADRS and CGI-I/CGI-S performed on OC data was in line with the results presented above (Tables 48 to 51).

Pharmacokinetic Results

- The plasma concentration results are summarized below:

Time	**N**	**Median (ng/mL)**	**Mean (ng/mL)**	**S.D. (ng/mL)**	**Min (ng/mL)**	**Max (ng/mL)**
Day 0 - 2hrs post-IV	38	11.15	13.91	13.43	0.97	86 5
Day 0 - bedtime	39	9.68	9.51	2.83	3.78	15.7
Day 1	38	9.64	9.93	2.78	4.4	15.9
Day 7	38	9.85	11.93	5.95	3.87	27.6

- The steady-state plasma exposure levels of vortioxetine were reached on Day 0 and were maintained at approximately the same level to Day 7. The obtained plasma exposure of vortioxetine was comparable to that following 2 weeks of oral administration of 15mg/day vortioxetine. No further analyses of the population pharmacokinetic parameters was performed.

Safety Results

Adverse events

- An overview of adverse events with an onset in the PBO Lead-in Period, the DBT Period and the Safety Follow-up Period are presented in Tables 52 to 54.
- An overview of adverse events with an onset in the DBT Period is presented below and in Table 53:

	PBO		VOR	
	n	**(%)**	**n**	**(%)**
Patients treated	41		39	
Patients who died	0		0	
Patients with treatment-emergent SAEs	0		0	
Patients with TEAEs	15	(36.6)	21	(53.8)
Patients with TEAEs leading to withdrawal	0		0	
Total number of TEAEs	28		44	

- Adverse events in the Placebo Lead-in Period and in the DBT Period are summarized by preferred term in Tables 55 and 56, respectively, and by system organ class (SOC) and preferred term in Tables 57 and 58, respectively.
- The TEAEs are summarized by preferred term in Tables 59 and 60 for the PBO Lead-in Period and the DBT Period, respectively. All of the TEAEs were *mild* to *moderate*. Most of the TEAEs were considered *related* to IMP; these are summarized by preferred term and intensity in Table 61 (PBO Lead-in Period) and Table 62 (DBT Period). The most common TEAEs (TEAEs occuring more than 3 times) in the DBT Period were *nausea*, *erythema*, *dizziness*, *sedation* and *somnolence*. In the first 24 hours of the DBT period, the incidence of TEAEs was almost double as high in the VOR group (49%) as in the PBO group (27%), and the number of patients having *nausea* in the VOR group was also double as high as in the PBO group (4 patients [VOR] versus 2 patients [PBO]) (Table 63). For the total DBT period, *nausea* was more common in the PBO group than in the VOR group (7 patients [PBO] versus 5 patients [VOR]) (Table 60).
- The TEAEs of special interest with an onset in the DBT Period are summarized by SOC and preferred term in Table 64. In general, the incidences of TEAEs of special interest were similar across treatment groups. A comparable proportion of patients in each treatment group had *nausea* (13% [5 patients]) in the VOR group and 17% (7 patients) in the PBO group). One patient in the VOR group had 3 incidences of *vomiting*, 1 patient in the VOR group had *pruritus* and 1 patient in the VOR group had *pruritus allergic*. Three patients (1 in the PBO group and 2 in the VOR group) had *diarrhoea*. No patients had *constipation* or *sexual dysfunction*.
- Adverse events with an onset in the PBO Lead-in Period are listed in Listing 4, adverse events in the DBT Period are listed in Listing 5. Serious adverse events (SAEs) with an onset in the Safety Follow-up Period are listed in Listing 6. The only SAE that occurred in the study was assessed as *not related* to the IMP, for details, refer to the individual narrative in *Narrative of SAEs*.

Clinical Laboratory Test Results

- The clinical safety laboratory values and the mean changes from Baseline therein are summarized for all patients in Tables 65 to 69. There were no clinically relevant mean changes from Baseline in the clinical laboratory values.
- The proportion of patients with out of range and PCS clinical safety laboratory values are summarized in Tables 70 and 71.
- The reference ranges and PCS criteria are in Listing 7. All patients with PCS laboratory values are listed in Listing 8 and Table 71 and adverse events in patients with PCS values are presented in Listing 9. The proportion of patients with post-Baseline PCS laboratory values were similar across the treatment groups.
- The results of the microscopic examinations of urine in patients with abnormal urine dipstick findings are presented in Listing 10. The results of the microscopic examinations were similar across the treatment groups.

Safety Results, continued

Vital Signs

- Vital signs in the PBO Lead-in Period and in the DBT Period, and changes from Baseline therein, are summarized in Tables 72, 73 and 74, respectively. The reference ranges and PCS criteria for vital signs are in Listing 11.
- The proportion of patients with out of normal range and PCS vital signs in the PBO Lead-in Period and the DBT Period are summarized in Tables 75 and 76, respectively. One patient in the VOR group had PCS low diastolic blood pressure 2 hours after receiving the vortioxetine IV infusion. The PCS low diastolic blood pressure resolved the following day (Day 1). No other patients had PCS vital signs in this study. The PCS values and adverse events for this patient are presented in Listings 12 and 13, respectively.

ECGs

- The investigators evaluation (*normal*/*abnormal*) of ECG parameters and the ECG values are summarized in Tables 77 and 78 respectively. The majority of patients had normal ECGs as evaluated by the investigator. The proportion of patients with normal relative to abnormal (but not clinically significant) ECGs was comparable between the treatment groups. The reference ranges and PCS criteria for ECGs are in Listing 14. There were no PCS ECG parameter values in this study (Table 79).

Assessment of liver parameters

- Only two patients (one in the PBO group and one in the VOR group) had elevated liver parameters in the DBT Period, these are summarized in Listing 15. No patients fulfilled Hy's law.

Assessment of Suicidality

- The C-SSRS scores based on the Baseline/Screening version for the lifetime of the patient at time of enrolment and for the past 6 months are summarized in Tables 80 and 81, respectively. The C-SSRS scores were as expected for the patient population, and there were no major differences between the two treatment groups. The C-SSRS scores based on the *Since Last Visit* version for the DBT Period are summarized in Table 82. The majority (95%) of the patients had had no suicidal ideation or behaviour, except for two patients in the PBO group who scored 1 (corresponding to *wish to be dead*).
- The changes from Baseline in CGI-SS score at Day 1, 3 and 7 are summarized in Table 83. There was no change from Baseline in the CGI-SS scores at any of the tested days, and no difference between the treatment groups. The CGI-SS Improvement scores at Day 1, 3 and 7 were in accordance with the CGI-SS scores, with a mean CGI-SS Improvement score of 4 points (corresponding to *no change*) at all tested days (Table 84).

Conclusions

- In the primary efficacy analysis, based on the change from Baseline to Day 1 in MADRS-6 subscale score, the combined treatment with VOR IV + VOR oral was not statistically significantly superior to the combined treatment with PBO IV + PBO oral. The key secondary and the secondary analyses corroborated this conclusion.
- The VOR 25 mg IV followed by VOR 10 mg/day dosing regimen was safe and well-tolerated in this one week study in patients with MDD.

Report Date

16 April 2020

This study was conducted in compliance with *Good Clinical Practice*.